Sleep Medicine Reviews 18 (2014) 349–356

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Attention deficit hyperactivity disorder and sleep disordered breathing in pediatric populations: A meta-analysis

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ARTICLE INFO

Article history:
Received 13 July 2013
Received in revised form
25 November 2013
Accepted 15 December 2013
Available online 24 December 2013

Keywords:
Sleep disordered breathing
Obstructive sleep apnea
Attention deficit hyperactivity disorder
Meta-analysis

SUMMARY

A relationship between attention deficit hyperactivity disorder (ADHD) and sleep disordered breathing (SDB) in children and adolescents has been suggested by some authors. Yet, this topic remains highly controversial in the literature.

A meta-analysis was conducted in order to examine the extent of relationship between SDB and ADHD symptoms in pediatric populations and whether there are differences in ADHD symptoms pre- versus post-adenotonsillectomy in pediatric populations.

PubMed/Medline, PsychInfo and Cochrane databases were searched using the key words “attention deficit hyperactivity disorder” or “ADHD” and “obstructive sleep apnea” or “OSA” or “sleep disordered breathing” (SDB) or “SDB”. English language publications through September 2012 were surveyed. Meta-analysis was conducted to assess the relationship between SDB and ADHD symptoms in the first part of the study, and the extent of change in ADHD symptoms before and after adenotonsillectomy in the second part.

Eighteen studies satisfied the inclusion criteria for the first part of the study. This represented 1113 children in the clinical group (874 diagnosed with SDB who were examined for ADHD symptoms; 239 diagnosed with ADHD who were examined for SDB) and 1405 in the control-group. Findings indicate that there is a medium relationship between ADHD symptoms and SDB (Hedges’ $g = 0.57$, 95% confidence interval: 0.36–0.78; $p = 0.000001$). A high apnea hypopnea index (AHI) cutoff was associated with lower effect sizes, while child age, gender and body mass index did not moderate the relationship between SDB and ADHD. Study quality was associated with larger effect sizes. In the second part of the study, twelve studies were identified assessing pre- versus post-surgery ADHD symptoms. Hedges’ g was 0.43 (95% confidence interval = 0.30–0.55; $p < 0.001$; $N = 529$) suggesting a medium effect, as adenotonsillectomy was associated with decreased ADHD symptoms at 2–13 months post-surgery.

The findings of this meta-analysis suggest that ADHD symptoms are related to SDB and improve after adenotonsillectomy. Therefore, patients with ADHD symptomatology should receive SDB screening. Treatment of comorbid SDB should be considered before medicating the ADHD symptoms if present.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric syndrome affecting 3–16% of school children with world prevalence of 5.29% [1]. It is characterized by inattention, hyperactivity, and/or impulsivity, occurring in at least two different settings, and often leads to academic, social, and occupational dysfunction [2]. Although the diagnosis of ADHD is best made through a clinical interview, rating scales completed by teachers and parents have been utilized and shown to be valid [3]. The variation of diagnostic criteria for ADHD over the years (i.e., using different versions of Diagnostic and Statistical Manual for Mental Disorders or International Classification of Diseases criteria), the source of informant (e.g., parent, teacher, or clinical), and the reliability of rating scales to aid in diagnosis render this diagnosis difficult in some instances [4]. Other psychiatric disorders can also mimic ADHD symptomatology (e.g., anxiety), as may sleep disorders, thus complicating the diagnosis of ADHD.

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1087-0792/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.smrv.2013.12.003

Sleep disordered breathing (SDB) in children is a disorder varying from primary snoring (PS) at the least severe end of the spectrum to upper airway resistance syndrome (UARS), obstructive hypoventilation, and obstructive sleep apnea (OSA) in more severe cases. UARS is characterized by partial upper airway obstruction without oxygen desaturation, and is also associated with respiratory event related arousals and more negative esophageal pressure. OSA diagnosis depends on the apnea/hypopnea index (AHI), which is the average number of respiratory apneas and hypopneas per hour of sleep. Grading of the sleep apnea syndrome in children differs from adults; although recommended cutoffs have varied over time, it is generally agreed that an AHI $\geq$1/h is abnormal [5]. Mild cases of OSA range from 1 to 5 per hour, with moderate cases ranging from 5 to 10 per hour, and severe cases above 10 per hour. Although the recommendations set by the American Academy of Sleep Medicine (AASM) in 2007 specified the criteria of using two missed breaths equivalent duration to diagnose respiratory events, the AHI cutoff limit to diagnosing OSA remains controversial [6].

Several studies suggest an elevated incidence of SDB, ranging from 25 to 57%, among children and adolescents diagnosed with ADHD symptoms [7–13]. Other studies, however, question this relationship as they find no such elevated incidence of ADHD symptoms associated with SDB [14–17]. Small sample sizes, lack of polysomnographic (PSG) diagnosis of SDB, variability between studies on AHI cutoffs used to diagnose SDB (e.g., some used a cutoff of $>$ 5 per hour, while others used $>$ 1 per hour), and variability in whether a clinical diagnosis of ADHD or an ADHD rating scale was used to assess ADHD symptoms might explain some of the inconsistency in outcomes.

SDB during sleep is usually associated with lower oxygen saturations. This intermittent hypoxia/hypercapnia, with consequent sleep interruption might have an impact on brain development and affect cognitive function [18], leading to inattention [19]. Children diagnosed with SDB have been found to have elevated levels of inflammatory cytokines (C-reactive protein and interleukin-6), which also might contribute to poor cognitive function, including poor attention span [20,21].

Due to the inconsistent relationship between SDB and ADHD symptoms, further research is needed to address the extent to which they are related. An improved understanding of this relationship is important as it may have clinical implications. For example, children suffering from mild OSA and ADHD, treated with adenotonsillectomy (AT; the main treatment for SDB in children) had comparable improvements in ADHD symptoms to those treated with methylphenidate in one study [22]. This finding suggests that at least for some children with comorbid SDB, ADHD symptoms can improve with AT surgery without the need for long-term drug treatment. Although possible, it remains unclear whether AT surgery would lower the medication dosage needed for those with residual ADHD symptoms. Early identification and treatment for SDB might prevent permanent life-long disability and financial loss. Using meta-analysis, the current review examines the relation between ADHD and SDB among children and adolescents.

Methods

Study selection

A PubMed/Medline, PsychInfo and Cochrane library search was performed using the terms "attention deficit hyperactivity disorder" or "ADHD", "attention problems" and "obstructive sleep apnea" or "OSA" or "sleep disordered breathing" or "SDB" crossed by "child", "children" and "adolescent". Google Scholar was also used to facilitate the search results. References cited in these articles were also examined and included if they met study criteria. English language studies through September 2012 were examined.

Inclusion and exclusion criteria

Since this study focuses on the pediatric population, only patients aged from 0 to 18 years old were included. No study was included if the oldest individual was older than 18 years of age.

Although there are several proposed methods to diagnose SDB including the pediatric sleep questionnaire (PSQ), the gold standard diagnostic test remains polysomnography (PSG) [23]. Thus, studies having PSG performed in both clinical and control groups were required for inclusion in the first part of the study. Parent and/or teacher ADHD symptom rating scales or clinician-based ADHD diagnosis were used to assess ADHD symptoms in these subjects. Studies were only included if there was a control group. Authors of studies with missing information were contacted; these studies were only included if sufficient information to compute an effect size (ES) was provided by the researcher. In the second part of the meta-analysis, PSG was required to be done both before and 1–13 months after adenotonsillectomy. ADHD symptomatology was also assessed during the same time frame at both baseline and post-surgery.

Identification of appropriate studies was conducted by the first author (K.S.) and was reviewed by the second author (D.B.). For the first part of the meta-analysis, 48 published studies were initially identified, with ten excluded due to lack of the use of PSG to detect SDB at least in one group [8,9,24–31]. Five others lacked a control group and were excluded [14,32–35]. Another five were excluded for the following reasons: one study selected only for children who had both OSA and ADHD in the clinical group [22], one study did not specify the relationship between AHI and ADHD symptoms [36], one had PSG done but did not present AHI results [10], and two used excessive daytime sleepiness rather than SDB; this latter symptom can originate from a variety of causes other than SDB and was thus excluded [37,38]. In yet another study, the authors used an unvalidated, two-item ADHD scale to compare the two groups; thus, this study was excluded [39]. In addition, data from one study was reported in four different publications; thus, data were used from these four studies [11,40–42] but reported as one study [11]. An additional four studies also appeared to have patient overlap [13,43–45]. After contacting two authors, the extent of patient overlap could not be resolved as one author suggested common patients among two studies [43,44], while another suggested common patients among each of the four. Thus, two different analyses were conducted: one including three out of the four studies and another only including the study with the greatest number of patients in both the OSA and control groups. To minimize positive selection bias of publication, we searched for unpublished studies and identified two dissertations [46,47], both of which had a related publication already identified, one of which was included in the meta-analysis [48]. The other was excluded due to the lack of PSG. In the second part of the study, 12 studies satisfied the selection criteria and were included for meta-analysis [11,13,22,30,33,41,44,45,49–55].

Data extraction

Data from the remaining 20 studies were coded by one author (K.S.) and reviewed by the second (D.B.) for accuracy in the initial part of the study [11–13,15–17,40,41,44,45,48,49,56–65]. Coded information included: sample size, type of clinical group, age, gender, body mass index (BMI), AHI cutoff, and study quality for both clinical and control groups. In the second part, pre- and post-AT ADHD symptoms levels were recorded and differentiated.

Table 1
Studies examining the relation between ADHD symptoms and SDB.

Study Name, year	Variable in clinical group	ADHD and/or OSA depended on	# Clinical subjects	# Control subjects	Mean/SD (age clinical group, y)	Mean/SD (age control group, y)	BMI clinical (kg/m^2)	BMI control (kg/m^2)	Male% clinical group	Male% control group
Barnes et al., 2012 [64]	OSA	CBCL	14	14	6.2 ± 1.81 (4–8)	6.2 ± 1.3 (4–8)	19.4 ± 4.79	17.1 ± 2.5		
Beebe et al., 2010 [65]	SDB	BASC	126	37	13.7 ± 1.9 (10–16.9)	13 ± 2 (10–16.9)	39 ± 7.5	35.9 ± 6.5		
Blunden et al., 2000 [56]	PS + one case of OSA	CBCL	16	16	7.2 ± 1.6 (5–11)	7.7 ± 1.6 (5–11)			43.8	43.8
Bourke et al., 2011 [57]	PS/OSA	CBCL/BRIEF	99	35	9.6 ± 1.5 (7–12)	9.5 ± 1.8			59.3	48.6
Chervin et al., 2001 [15],[a]	SDB	CPRS (hyperactivity index t-score); Clinician Dx	59	54	9.6 ± 3.7 (2–18)	10.1 ± 4.4			66	63
Chervin et al., 2006 [40]	AT/OSA	CPRS, CSI, CPT	40	27	7.8 ± 1.8	9.3 ± 2		18.9 ± 2.9	52.5	70.4
Cooper et al., 2004 [17]	ADHD	CBCL, CPRS, CPT, Clinician Dx	18	20	10.5 ± 3 (6–16)	10 ± 3.9 (4–16)			83.3	55
Galland et al., 2011 [16]	ADHD	Clinician Dx,	28	28	10.1 (6–12)	10.2 (6–12)	18.7 ± 3.9	18.7 ± 3.5	78.6	78.6
Golan et al., 2004 [59]	ADHD/OSA	Clinician Dx, OSA Dx according to AHI level with cutoff AHI ≥ 1/h	34	32	12.4 ± 4.6	12 ± 3.6	20.4 ± 3.9	18.6 ± 2.2	76.5	65.6
Gottlieb et al., 2004 [58]	OSA	CPRS	61	144	5	5			51.7	
Huang et al., 2004 [12]	ADHD	CBCL, Clinician Dx	88	27	8.5 ± 1.9 (6–12)	9 ± 2 (6–12)	18.3 ± 3.7	20.0 ± 3.7	87.5	77.8
Kaemingk et al., 2003 [48],[a]	OSA	CPRS-R, Home sleep study	77	69	8.3 ± 1.8 (6–12)	8.4 ± 0.6			54.4	
Landau et al., 2012 [60]	OSA	CBCL, C-TRF	45	13	3.8 ± 9.2 (2.5–5)	4.1 ± 0.7	15.7 ± 2	16.4 ± 2	73.3	46.2
Lewin et al., 2002 [49]	Mild/Sev OSA	CBCL	21	10	7.4 ± 2.7 (4–12)	6.9 ± 3.6 (4–9)	18.4 ± 4.9	16.3 ± 3.6	50	80
Miano et al., 2011 [61]	PS/OSA	ADHD rating scale	44	60	8.8 ± 1.9	9.8 ± 2.4	18.6 ± 3.6	18.3 ± 1.8	60.5	36.7
O'Brien et al., 2003 [13],[a]	Mild ADHD	CBCL, CPRS	71	39	6.5 (5–7)	6.5 (5–7)				
O'Brien et al., 2003 [44]	ADHD	Clinician Dx	100	49	7.2 ± 0.9	6.7 ± 0.4			66	44
O'Brien et al., 2004 [45]	SDB	CPRS, CBCL	35	35	6.7 ± 0.6 (5–7)	6.7 ± 0.5 (5–7)	19.8 ± 4.3	17.7 ± 3.5	49	49
Rosen et al., 2004 [62]	OSA	CBCL, CPRS	40	667	9.3 ± 0.9 8–11)	9.5 ± 0.8	19 ± 4.7	17.9 ± 3.5	42.5	50.2
Ting et al., 2011 [63]	OSA	CBCL, TRF	128	10	10.2 ± 1.2	10.1 ± 0.9	18.4 ± 3.2	17.1 ± 0.8	63.3	40

ADHD: Attention Deficit Hyperactivity Disorder; BRIEF: Behavior Rating Inventory of Executive Function; CBCL: Child Behavior Check List; CPRS: Conner's parent rating scale; CPT: Auditory continuous performance test; CRPS-R: Conners' Parent Rating Scales-Revised; CSI: child symptom inventory; CTRS: Conner's teacher rating scale; C-TRF: caregiver teacher report; NEPSY: neuropsychological assessment; OSA: obstructive sleep apnea; PS: primary snoring; SD: Standard Deviation; SDB: sleep disordered breathing includes PS and OSA.

[a] Studies that used AHI cutoff ≥5/h to diagnose OSA.

Data analysis

Data from the studies were analyzed using the Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ) software program. Hedges' g is an effect size statistic that represents the standardized difference between two groups. It was computed using a random effects model, with 95% confidence intervals (CI) reported. The results were plotted on a Forrest graph to provide an overview of the results. Homogeneity between studies was tested using Q, while I^2 index assessed the degree of their heterogeneity, estimating the total variation across studies caused by heterogeneity rather than chance. A value of I^2 around 25% suggests low heterogeneity, 50% as moderate, while 75% suggests high heterogeneity. Publication bias was evaluated by examining the relationship between standard errors of the means and the effect sizes and was estimated by the Kendall's tau value. To assess the potential moderator effects of age, gender, BMI, study quality, and AHI cutoff, the mean for each variable was computed for each study and weighted by sample size, and then analyzed in Statistical Product and Service Solutions (SPSS)® using linear regression analyses using inverse variances as weights. Study quality was assessed using the Newcastle–Ottawa Scale for case–control studies [66]. This scale has eight items divided into three different categories: selection, comparability and exposure. Each item is graded with a point, if it satisfies certain level except comparability which can have up to two points. Thus, a total score for study quality can range from zero to a maximum of nine points.

Results

Question 1: Is there a relationship between SDB and ADHD symptomatology?

Eighteen studies were included in the analysis constituting a total of 1113 children in the clinical group (mean number per study is 62) that were compared to 1405 in the control group (with mean of 78 individuals in each study; see Table 1). The mean unweighted age for the clinical group was 8.37 years (SD = 2.32) and 8.54 years (SD = 2.23) for the controls. The clinical groups consisted of two: one in which children with SDB (874 individuals) were evaluated with ADHD rating scales and compared to controls; the second in which children diagnosed with ADHD (239) were administered PSG and compared to controls.

Aggregate effect sizes and homogeneity tests

The overall ES (Hedges' g) for the eighteen studies assessing the relation between ADHD symptoms and SDB was 0.57 (95% CI = 0.36–0.78; $p = 0.00001$; see Fig. 1). After the inclusion of the other two studies [44,45], raising the overall number of studies to twenty, the overall ES for the relation between ADHD symptoms and SDB was 0.53 (95% CI = 0.34–0.72; $p = 0.00001$). Thus, it does not appear that the addition of these two studies would have changed the results significantly. Of note, one of the excluded studies [39] used an unvalidated ADHD measure but had an ES of 0.67 (CI = 0.44–0.90; $p \leq 0.001$) similar to 0.57, suggesting that exclusion of this study also did not greatly affect the overall

reported ES. Testing for heterogeneity, the Q value with 17 d.f. was 71.30, signifying considerable heterogeneity across studies, while I^2 was 76.16, $p < 0.001$, confirming this high degree of heterogeneity. Therefore, we tested several potential moderators as possible sources of this heterogeneity. In addition, Kendall's tau = 0.25; $p = 0.15$; this suggests that the standard errors of the means and the effect sizes were independent, suggesting that there was no significant publication bias.

Moderator analyses

Utilizing a mean weighted ES among the eighteen studies to assess for moderator effects, significant moderation was found for AHI scores such that studies using a higher AHI cutoff had lower ESs (beta = −0.61, $p = 0.007$). Among the five studies using a high AHI cutoff (i.e., AHI of ≥4–5/h), the ES was 0.26 (95% CI = 0.08–0.44; $p = 0.004$) [13,15,48,58,62]. This was compared to the rest of the studies using a lower AHI cutoff (i.e., AHI ≥ 1), which had a higher ES of 0.72 (95% CI = 0.46–0.99; $p = 0.0000001$). A significant moderation effect also was found for study quality as studies of better quality had larger ESs (beta = 0.48, $p = 0.045$). No significant moderation was found for age (beta = 0.07, $p = 0.80$), gender (beta = −0.33, $p = 0.25$) or BMI (beta = 0.34, $p = 0.42$). We also examined whether ESs were greater for inattention than for hyperactivity symptoms, using four studies that assessed both sets of symptoms [48,61,62,65]. The mean ES for hyperactivity symptoms with OSA was 0.54 (95% CI = 0.05–1.03; $p = 0.03$), while the mean ES for inattention symptoms was similar at 0.50 (95% CI = 0.03–0.98; $p = 0.038$). These subscales were not significantly different and suggest that the type of ADHD symptoms does not moderate the relationship between ADHD and OSA.

Question 2: Is there any difference between ADHD symptomatology pre- versus post-AT?

In the second part of the study, which involved 529 individuals, ADHD symptoms were compared before surgery versus post-AT among children with SDB (see Table 2). Hedges' g was 0.43 (95% CI = 0.30–0.55; $p < 0.001$), indicating a medium improvement in ADHD symptoms from pre- to post-surgery (see Fig. 2). Testing for heterogeneity, the Q value with 11 d.f. was 10.03, signifying minimal heterogeneity across studies.

Discussion and conclusion

Pediatric populations suffering from SDB are at increased risk of presenting with symptoms of ADHD, including inattention and hyperactivity. The ES of 0.57 found in the current meta-analysis suggests that a medium relationship exists between SDB and ADHD symptoms. Moreover, a medium improvement was found in ADHD symptoms following adenotonsillectomy (ES = 0.43).

Substantial heterogeneity was observed across studies, including across prior meta-analyses. Of the two prior meta-analyses examining SDB and ADHD symptoms, which were based on much smaller samples of children, one found a medium ES similar to ours meta-analysis [67]. Because the authors used strict criteria in defining group membership (e.g., they excluded studies in which children had comorbid psychiatric diagnoses aside from oppositional behavior, and also excluded those whose ADHD was treated with medication), only three studies that were also included in our meta-analysis were included in their review. Their findings, however, were consistent with those of the current, larger meta-analysis as they reported an overall effect size of 0.52 (CI = 0.23–0.81) across the three studies. In the second meta-analysis differentiating AHI in children with ADHD versus controls, a smaller ES (Cohen's d) of 0.10 was found (95% CI = −0.40 to 0.60), suggesting no relationship between AHI scores in OSA patients and ADHD symptoms [4]. Their meta-analysis, however, was published in 2006 and limited to only four studies totaling 227 children in the ADHD group versus 132 in the control group. Since these two prior meta-analyses were conducted earlier, they were unable to include a number of recent publications addressing the relationship between SDB and ADHD symptoms.

In the large prospective TuCASA study of children 6–12 years of age [68], an overall ES of 0.31 was found between respiratory disturbance index (high vs. low) and parent ratings of children's

Study name	Sample size: Clinical	Sample size: Control	Hedges's g	Variance	Lower limit	Upper limit	p-Value
Barnes et al., 2012[64]	14	14	0.81	0.15	0.05	1.57	0.0365
Beebe et al, 2010[65]	126	37	0.52	0.04	0.13	0.91	0.0093
Blunden et al., 2000[56]	16	16	0.65	0.13	-0.05	1.34	0.0678
Bourke et al., 2011[57]	99	35	1.03	0.04	0.63	1.44	0.0000
Chevrin et al., 2001[15]	59	54	0.03	0.04	-0.34	0.40	0.8756
Chevrin et al., 2006[40]	40	27	0.43	0.06	-0.07	0.92	0.0894
Cooper et al., 2004[80]	18	20	0.22	0.11	-0.42	0.86	0.4983
Gallard et al., 2001[16]	28	28	0.27	0.07	-0.26	0.79	0.3188
Golan et al., 2004[59]	34	32	0.67	0.06	0.18	1.17	0.0080
Gottlieb et al., 2004[58]	61	144	0.53	0.02	0.23	0.84	0.0006
Huang et al., 2004[12]	88	27	1.24	0.06	0.77	1.71	0.0000
Kaemingk et al., 2003[48]	77	69	0.05	0.03	-0.27	0.38	0.7575
Landau et al., 2012[60]	68	36	0.23	0.04	-0.17	0.63	0.2644
Lewin et al., 2002[49]	21	10	0.81	0.15	0.05	1.58	0.0358
Miano et al., 2011[61]	44	60	1.80	0.05	1.34	2.26	0.0000
O'Brien et al, 2004[13]	100	49	0.29	0.06	-0.17	0.75	0.2188
Rosen et al., 2004[45]	121	708	0.29	0.01	0.09	0.48	0.0036
Ting et al., 2011[63]	128	10	0.64	0.11	-0.00	1.29	0.0504
			0.57	0.01	0.36	0.78	0.0000

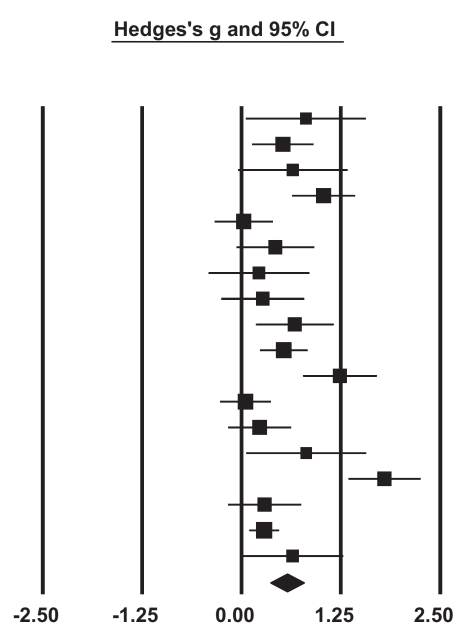

Fig. 1. Randomized effect size (Hedges' g) for the relationship between attention deficit hyperactivity disorder (ADHD) symptoms and sleep disordered breathing (SDB).

Table 2
Studies examining ADHD symptoms both before and after adenotonsillectomy.

Study Name, year	ADHD scale used	# Pre-AT	# Post-AT	Mean/SD age (age range)	Duration between assessment (months)	Pre-AT (#/h)	Post-AT AHI (#/h)	Cut-off/h	Male%
Chervin et al., 2012 [55]	CPRS & CSI	81	81	7.8 ± 2.8	7.2 ± 0.8	RDI = 7.5 ± 11.1	2.1 ± 1.8		54.32
Dillon et al., 2007 [11]	DBDRS-combined	40	39		13.0 ± 1.4				
Galland et al., 2006 [30]	BASC-P	61	61	7.0 ± 2.0 (4–11)	3	AHI = 3.0 ± 2.6		AHI ≥ 1.5	57.38
Giordani et al., 2012 [41]	CPRS	40	39	7.8 ± 1.8	12	OAI = 1.5 ± 0.45	0.18 ± 0.45	OAI ≥ 0.5	52.5
Huang et al., 2007 [22]	CBCL-P & ADHD-RS	25	25	8.08 ± 1.28 (6–12)		AHI = 3.3 ± 1.1	0.89 ± 0.63	AHI ≥ 1	92.0
Lewin et al., 2002 [49]	CBCL	7	7	(4–12)	6–18	RDI = 17.4 ± 9.9		RDI ≥ 10	
Li et al., 2006 [33]	CBCL	40	40	8.4 ± 1.6	6	AHI = 10.6 ± 11.1	1.7 ± 2.1	AHI ≥ 1	90.0
Mitchell et al., 2005 [50]	BASC	52	52	7.1 (5–88)	4.4	AHI = 16.2		AHI ≥ 5	56
Mitchell et al., 2006 [51]	BASC	23	23	7.2 (2.5–14.8)	2.4	AHI = 14.1		AHI ≥ 5	65
Mitchell et al., 2007 [52]	BASC	40	40	7.07	6	AHI = 15.9		AHI ≥ 5	55
Mitchell et al., 2009 [53]	BASC	89	89	(3–17.1)	3–6	AHI = 16.3	4.7	AHI ≥ 2	60.67
Tran et al., 2005 [54]	BASC	31	31	5.8 ± 2.5 (2–11.5)	5.4 ± 1.9			RDI ≥ 5 or AHI ≥ 1	60

ADHD: Attention deficit hyperactivity disorder; ADHD-RS: ADHD rating scale; AHI: apnea hypopnea index; AT: adenotonsillectomy; BASC-P: behavioral assessment scales for children (parent); CBCL: child behavior checklist; CPRS: Conner's parent rating scale; CSI: child symptoms inventory; DBDRS: disruptive behavior disorders rating scale; OAI: obstructive apnea index; RDI: respiratory disturbance index.

ADHD symptoms. This study was not included in the current meta-analysis because a somewhat arbitrary cut-off was made between what constituted a high vs. low RDI score (i.e., "high" represented the highest 15%, while "low" represented the lowest 85%), but the study's ES, while somewhat lower than that found in our meta-analysis, was significant and indicated a small to medium relationship between SDB and ADHD symptoms. Guidelines for diagnosing pediatric OSA were published in 2007, after this study was completed [6].

Several potential moderators of the relation between ADHD symptoms and SDB were examined in the current meta-analysis. Study AHI cutoff was found to moderate the ADHD–SDB relationship such that studies using lower AHI cutoffs actually had higher ESs. There are five studies utilizing an AHI cutoff of ≥4–5/h to diagnose OSA; two of these studies did not find a relation between ADHD symptoms and SDB/OSA. This suggests that the milder form of OSA might actually be more closely related to ADHD symptoms, although the reason for this finding is unclear. Study quality also was found to be a significant moderator as higher quality studies had larger ESs, suggesting that the ADHD–SDB relationship is not an artifact of poorer quality studies.

Adenotonsillectomy remains the main treatment for OSA in the pediatric population with enlarged lymphoid tissue. A recent relatively large, randomized trial of 210 children, age 5–9 y was not included in the current meta-analysis because researchers compared the caregiver and the teacher ratings for children using a global rating scale of psychopathology as opposed to one focusing specifically on ADHD symptoms [69]. Similar to our findings for ADHD symptoms, however, a mild to moderate decrease was observed in the global rating scale as assessed by both groups (caregiver ES = 0.28; teacher's ES = 0.37), raising the possibility that symptoms other than ADHD symptoms might also be improved following adenotonsillectomy. Consistent with this hypothesis, a recent meta-analysis found depressive symptoms to decrease significantly among children and adolescents with SDB who underwent adenotonsillectomy [70].

There are several possible explanations for the relationship between SDB and ADHD symptoms. SDB syndrome is associated with lower oxygen saturations and hypercapnia overnight, oxidative stress, increased free radicals, and/or release of inflammatory cytokines (e.g., proinflammatory cytokines interleukin-6 and tumor necrotizing factor alpha) leading to neurological dysfunction particularly involving certain brain areas (e.g., prefrontal cortex [20,21,71]). Cortical dysfunction is associated with cognitive and behavior dyscontrol and can consequently lead to inattention,

Study name	Sample size: Pre-AT	Post-AT	Statistics for each study: Hedges's g	Variance	Lower limit	Upper limit	p-Value
Chervin et al., 2012[55]	81	81	0.40	0.03	0.09	0.71	0.012
Dillon et al., 2007[11]	40	39	0.15	0.05	-0.28	0.59	0.490
Galland et al., 2006[30]	61	61	0.43	0.03	0.07	0.78	0.019
Giordani et al., 2012[41]	40	39	0.26	0.05	-0.18	0.70	0.250
Huang et al., 2007[22]	25	25	0.83	0.09	0.25	1.41	0.005
Lewin et al., 2002[49]	7	7	0.43	0.26	-0.57	1.42	0.400
Li et al., 2006[33]	40	40	0.31	0.05	-0.13	0.75	0.164
Mitchell et al., 2005[50]	52	52	0.45	0.04	0.06	0.83	0.024
Mitchell et al., 2006[51]	23	23	0.56	0.09	-0.02	1.14	0.058
Mitchell et al., 2007[52]	40	40	0.84	0.05	0.39	1.29	0.000
Mitchell et al., 2009[53]	89	89	0.58	0.05	0.16	1.00	0.007
Tran et al., 2005[54]	31	31	0.09	0.06	-0.41	0.58	0.735
			0.43	0.00	0.30	0.55	0.000

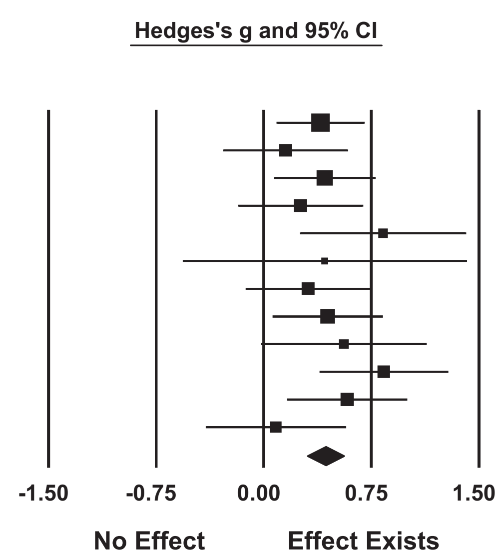

Fig. 2. Pre- versus post-adenotonsillectomy (AT) as compared by the attention deficit hyperactivity disorder (ADHD) symptom level. Group-A signifies pre-AT while group-B is post-AT.

hyperactivity or impulsivity symptoms [72]. SDB also frequently leads to sleep fragmentation, thus, rendering the child exhausted and cognitively impaired during the day [47]. It is also well known that obesity can lead to or worsen SDB in both pediatric and adult populations [73]. This might be secondary to fat deposition in the neck causing narrow airway and/or a decrease in lung functional capacity due to truncal obesity. Obese children have a higher incidence of SDB and excessive daytime sleepiness (EDS) symptoms. This might be explained by the micoawakenings occurring at nighttime and oxygen desaturation, thus leading to EDS. It has been hypothesized that children with EDS compensate for their sleepiness by increased motor activity, thus presenting with what appear to be ADHD symptoms [74].

Given that SDB co-occurs with children's ADHD symptoms, a thorough clinical sleep evaluation should occur among children presenting with ADHD symptoms. Currently, many of these children are likely being treated for their ADHD symptoms with medication. It remains controversial as to whether treating associated OSA would cure or improve ADHD. Adenotonsillectomy, a commonly performed surgery today utilized to treat OSA, is relatively simple and improves up to 85% of children with SDB. Also, while ADHD symptoms may remain for some children, it is possible that improvement in SDB may allow for the use of lower medication doses to treat such residual ADHD symptoms.

Several limitations to the current meta-analysis, which incorporated a relatively large number of studies to estimate the ES between SDB and ADHD symptoms, deserve mention. Inclusion and exclusion criteria varied among different studies; e.g., some studies excluded individuals with a history of SDB or ADHD symptoms while others included them. Similarly, some studies included children with primary snoring in their SDB group, while others did not. Such study differences may affect the ES between SDB and ADHD symptoms. Furthermore, most studies focused on the use of clinical rating scales rather than diagnostic criteria per se, so it is unknown whether results would differ if data was based on diagnostic interviews or clinician diagnoses. Articles utilizing neuropsychological measures of attention were excluded as they generally correlate poorly with ADHD [75]. There are 21 studies that were excluded for this reason, most of which did not find a significant relation between SDB and ADHD symptoms [76]. Inclusion of these studies in the meta-analysis would have lowered the ES. Finally, most of the studies excluded most of the major medical and neurological problems. However, most of the studies did not directly comment on the comorbid psychiatric problems. Because included studies did not report on the presence of restless leg syndrome (RLS), a disorder with higher prevalence in children with ADHD, it is possible that the relationship between SDB and ADHD symptoms might be related to RLS symptoms and should be examined in future research [77].

Clinically, the present findings highlight the potential importance of screening children with ADHD symptoms for possible SDB symptoms. Of note, SDB is usually secondary to enlargement of the adenoids and the tonsils in most pediatric cases. This enlargement usually occurs between 2 and 8 years of age, coinciding with the typical onset of ADHD [78]. Thus, children diagnosed with ADHD symptoms in this age range might benefit from OSA/SDB screening. Such screening usually includes inquiries about snoring, observed apneas and waking up gasping for air. Oral examination shows enlarged tonsils, although adenoidal enlargement requires X-ray to facilitate diagnosis. Referral to a sleep specialist and PSG is required in cases with positive screening. AT is the treatment of choice with reassessment of the need for ADHD medication post-surgery.

Future research is needed to evaluate the ADHD symptom – SDB relation more extensively. For example, a better understanding of whether SDB is more closely related to ADHD symptoms or to symptoms of sluggish cognitive tempo, which is often closely related to ADHD [79] or other psychiatric problems such as depression [70], is needed. More generally, prospective studies are needed to identify children and adolescents who are being treated for ADHD, screen them for SDB, and then reevaluate them for improvement of ADHD symptoms and further medication adjustment. We would then be able to truly evaluate the impact of treating co-morbid SDB in patients with ADHD and develop further guidelines for diagnosing and managing children with ADHD and associated SDB.

Practice points

1) Children and adolescent patients suffering from SDB present with elevated rates of ADHD symptoms. A significant improvement in ADHD symptoms occurred in children and adolescents after adenotonsillectomy compared to pre-surgery.
2) Children and adolescents presenting with ADHD symptoms should be screened for SDB and, if present, treated for their SDB before to initiating psychotropic medication.
3) Treating SDB in children and adolescents with ADHD symptoms might eliminate or decrease the need for psychotropic medication use.

Research agenda

1) Further research is needed to evaluate the etiological reasons for the relationship between SDB and ADHD symptoms.
2) In this meta-analysis, ADHD scales were used to assess ADHD symptoms. ADHD scales, while correlated with ADHD diagnosis, do not necessarily indicate a diagnosis of ADHD. Thus, research is needed to examine whether the relation with SDB holds for children clinically diagnosed with ADHD.
3) Prospective studies are needed to identify children and adolescents who are being treated for ADHD, screen them for SDB, and then reevaluate them for improvement of ADHD symptoms and further medication adjustment.

Conflict of interest

None.

Acknowledgment

None.

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